

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/08849

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07H 21/04(2006.01);C12Q 1/68(2006.01)

USPC: 435/6,536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6,; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/0124600 (SIDRANSKY) 03 July 2003 (03.07.2003), see abstract, for example	1-67, 70
Y, P	US 2004/0146868 (COTTRELL et al.) 29 July 2004 (29.06.2004), see GSTP1 markers.	1-61, 70
Y	US 2004/0016006 A1 (JI et al.) 22 January 2004 (22.01.2004), see RASSF1A and RASSF1C, para 348.	1-61, 70
Y	US 2004/0048275 A1 (GULDBERG) 11 March 2004 (11.03.2004), see APC promoeter.	1-61, 70

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search
22 March 2006 (22.03.2006)

Date of mailing of the international search report

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-61 and 70

- Remark on Protest
- | | |
|--------------------------|---|
| <input type="checkbox"/> | The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee. |
| <input type="checkbox"/> | The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation. |
| <input type="checkbox"/> | No protest accompanied the payment of additional search fees. |

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-61, 70 drawn to a method for detecting a neoplasia using at least two promoters.

Group II, claims 62-68, 71-73 drawn to a kit comprising primers.

Group III, claim 69 drawn to a microarray.

Restriction Requirement Applicable to All Groups:

The claims are drawn to a method of analyzing a combination of promoters from several genes, namely two or more promoters. The product claims are drawn to primers for at least one promoter. A restriction is applied to each Group. A search of genes A and B, for example is distinct from a search for genes C and D.

The prior art teaches a method for detecting neoplasia in a biological sample by quantifying the promoter methylation of at least two promoters wherein the increase promoter methylation relative to a reference indicates the presence of neoplasia. Additionally, the prior art teaches a primer for the promoter which allows for methylation detection.

Specifically Guldberg (US 2004/0048275, March 11, 2004) teaches APC promoter methylation is responsible for aberrant accumulation of beta catenin in melanoma cells. Guldberg further teaches primers APC-MC-A and APC-MC-B which are used to detect methylation.

Sidransky (US 2003/0124600, July 3, 2003) teaches measuring the methylation of the promoter region of GSTP1. Sidransky teaches using real-time methylation specific PCR to determine the ratio between the level of methylation of a promoter region relative to the relative level of methylation of a region of a reference gene.

Ji (US 2004/0016006, January 22, 2004) teaches methylation status of the RASSF1A and RASSF1C promoter regions was determined by methylation-specific PCR to analyze lung cancer. Ji teaches that methylation-specific PCR352 primers for the RASSF1A 5' promoter region. The primers disclosed detect the methylated form (para 348).

Cottrell (US 2004/0146868, July 29, 2004) teaches GSTP1 markers within the promoter region that are useful for effectively distinguishing among benign hyperplasia of the prostate and different grades of prostate cancer.

Because the art teaches primers which allow for distinguishing methylation, there is no a contribution over the prior art. Further, the art teaches methylation in at least 2 promoters associated with neoplasia, thus, there is no contribution over the prior art.

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Continuation of B. FIELDS SEARCHED Item 3:

medline biosis caplus embase;

search terms: methylation, hypermethylation, hypomethylation; RASSF1A, RASSF1C, APC